

<110> UNIVERSITÉ DE MONTREAT

<120> NEW METALLOPROTEASES OF THE NEPRILYSIN FAMILY

<130> BIOMEP INC. NEPRILYSIN

<140> PCT/CA/00/00147

<141> 2000-02-11

<150> 2,260,376

<151> 1999-02-11

<160> 17

<170> PatentIn Ver. 2.1

<210> 1

<211> 750

<212> PRT

<213> Homo sapiens

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Val Leu Val Leu Leu Thr Ile Ile Ala Val Thr Met Ile Ala Leu 35 40 45

Tyr Ala Thr Tyr Asp Asp Gly Ile Cys Lys Ser Ser Asp Cys Ile Lys
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Ser Ala Ala Arg Leu Ile Gln Asn Met Asp Ala Thr Thr Glu Pro Cys 65 70 75 80

Thr Asp Phe Phe Lys Tyr Ala Cys Gly Gly Trp Leu Lys Arg Asn Val 85 90 95

Ile Pro Glu Thr Ser Ser Arg Tyr Gly Asn Phe Asp Ile Leu Arg Asp
100 105 110

Glu Leu Glu Val Val Leu Lys Asp Val Leu Gln Glu Pro Lys Thr Glu
115 120 125

Asp Ile Val Ala Val Gln Lys Ala Lys Ala Leu Tyr Arg Ser Cys Ile 130 135 140

Asn Glu Ser Ala Ile Asp Ser Arg Gly Glu Pro Leu Leu Lys Leu 145 150 150 155

Leu Pro Asp Ile Tyr Gly Trp Pro Val Ala Thr Glu Asn Trp Glu Gln 165 170 175

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Lys Tyr Gly Ala Ser Trp Thr Ala Glu Lys Ala Ile Ala Gln Leu Asn 180 185 190

Ser Lys Tyr Gly Lys Lys Val Leu Ile Asn Leu Phe Val Gly Thr Asp 195 200 205

Asp Lys Asn Ser Val Asn His Val Ile His Ile Asp Gln Pro Arg Leu 210 215 220

Gly Leu Pro Ser Arg Asp Tyr Tyr Glu Cys Thr Gly Ile Tyr Lys Glu 225 230 235 240

Ala Cys Thr Ala Tyr Val Asp Phe Met Ile Ser Val Ala Arg Leu Ile
245 250 255

Arg Gln Glu Glu Arg Leu Pro Ile Asp Glu Asn Gln Leu Ala Leu Glu 260 265 270

Met Asn Lys Val Met Glu Leu Glu Lys Glu Ile Ala Asn Ala Thr Ala 275 280 285

Lys Pro Glu Asp Arg Asn Asp Pro Met Leu Leu Tyr Asn Lys Met Thr 290 295 300

Leu Ala Gln Ile Gln Asn Asn Phe Ser Leu Glu Ile Asn Gly Lys Pro 305 310 315 320

Phe Ser Trp Leu Asn Phe Thr Asn Glu Ile Met Ser Thr Val Asn Ile 325 330 335

Ser Ile Thr Asn Glu Glu Asp Val Val Val Tyr Ala Pro Glu Tyr Leu 340 345 350

Thr Lys Leu Lys Pro Ile Leu Thr Lys Tyr Ser Ala Arg Asp Leu Gln 355 360 365

Asn Leu Met Ser Trp Arg Phe Ile Met Asp Leu Val Ser Ser Leu Ser 370 375 380

Arg Thr Tyr Lys Glu Ser Arg Asn Ala Phe Arg Lys Ala Leu Tyr Gly 385 390 395 400

Thr Thr Ser Glu Thr Ala Thr Trp Arg Arg Cys Ala Asn Tyr Val Asn 405 410 415

Gly Asn Met Glu Asn Ala Val Gly Arg Leu Tyr Val Glu Ala Ala Phe 420 425 430

Ala Gly Glu Ser Lys His Val Val Glu Asp Leu Ile Ala Gln Ile Arg 435 440 445

Glu Val Phe Ile Gln Thr Leu Asp Asp Leu Thr Trp Met Asp Ala Glu
450 455 460

Thr Lys Lys Arg Ala Glu Glu Lys Ala Leu Ala Ile Lys Glu Arg Ile 465 470 475 480

Gly Tyr Pro Asp Asp Ile Val Ser Asn Asp Asn Lys Leu Asn Asn Glu 485 490 Tyr Leu Glu Leu Asn Tyr Lys Glu Asp Glu Tyr Phe Glu Asn Ile Ile Gln Asn Leu Lys Phe Ser Gln Ser Lys Gln Leu Lys Lys Leu Arg Glu Lys Val Asp Lys Asp Glu Trp Ile Ser Gly Ala Ala Val Val Asn Ala 535 Phe Tyr Ser Ser Gly Arg Asn Gln Ile Val Phe Pro Ala Gly Ile Leu 550 Gln Pro Pro Phe Phe Ser Ala Gln Gln Ser Asn Ser Leu Asn Tyr Gly 570 Gly Ile Gly Met Val Ile Gly His Glu Ile Thr His Gly Phe Asp Asp 580 585 Asn Gly Arg Asn Phe Asn Lys Asp Gly Asp Leu Val Asp Trp Trp Thr Gln Gln Ser Ala Ser Asn Phe Lys Glu Gln Ser Gln Cys Met Val Tyr Gln Tyr Gly Asn Phe Ser Trp Asp Leu Ala Gly Gly Gln His Leu Asn 630 Gly Ile Asn Thr Leu Gly Glu Asn Ile Ala Asp Asn Gly Gly Leu Gly 645 650 Gln Ala Tyr Arg Ala Tyr Gln Asn Tyr Ile Lys Lys Asn Gly Glu Glu 665 Lys Leu Pro Gly Leu Asp Leu Asn His Lys Gln Leu Phe Phe Leu 675 680 Asn Phe Ala Gln Val Trp Cys Gly Thr Tyr Arg Pro Glu Tyr Ala Val Asn Ser Ile Lys Thr Asp Val His Ser Pro Gly Asn Phe Arg Ile Ile 710 715 Gly Thr Leu Gln Asn Ser Ala Glu Phe Ser Glu Ala Phe His Cys Arg Lys Asn Ser Tyr Met Asn Pro Glu Lys Lys Cys Arg Val Trp

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Leu Gly Thr Ile Leu Phe Leu Val Ser Gln Gly Leu Leu Ser Leu Gln 35 40 45

Ala Lys Gln Glu Tyr Cys Leu Lys Pro Glu Cys Ile Glu Ala Ala Ala 50 55 60

Ala Ile Leu Ser Lys Val Asn Leu Ser Val Asp Pro Cys Asp Asn Phe 65 70 75 80

Phe Arg Phe Ala Cys Asp Gly Trp Ile Ser Asn Asn Pro Ile Pro Glu 85 90 95

Asp Met Pro Ser Tyr Gly Val Tyr Pro Trp Leu Arg His Asn Val Asp 100 105 110

Leu Lys Leu Lys Glu Leu Leu Glu Lys Ser Ile Ser Arg Arg Asp 115 120 125

Thr Glu Ala Ile Gln Lys Ala Lys Ile Leu Tyr Ser Ser Cys Met Asn 130 135 140

Glu Lys Ala Ile Glu Lys Ala Asp Ala Lys Pro Leu Leu His Ile Leu 145 150 155 160

Arg His Ser Pro Phe Arg Trp Pro Val Leu Glu Ser Asn Ile Gly Pro 165 170 175

Glu Gly Val Trp Ser Glu Arg Lys Phe Ser Leu Leu Gln Thr Leu Ala 180 185 190

Thr Phe Arg Gly Gln Tyr Ser Asn Ser Val Phe Ile Arg Leu Tyr Val 195 200 205

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Ala Thr Leu Ser Leu Ala Val Arg Glu Asp Tyr Leu Asp Asn Ser Thr 225 230 235 240

Glu Ala Lys Ser Tyr Arg Asp Ala Leu Tyr Lys Phe Met Val Asp Thr 245 250 255

Ala Val Leu Leu Gly Ala Asn Ser Ser Arg Ala Glu His Asp Met Lys

Ser Val Leu Arg Leu Glu Ile Lys Ile Ala Glu Ile Met Ile Pro His 275 280 285

Glu Asn Arg Thr Ser Glu Ala Met Tyr Asn Lys Met Asn Ile Ser Glu 290 295 300

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Leu Ser Ala Met Ile Pro Gln Phe Asp Trp Leu Gly Tyr Ile Lys Lys

Tyr Asp Lys Asn Gly Asn Leu Asp Pro Trp Trp Ser Thr Glu Ser Glu 595 600 605

Trp Gly Thr Glu Tyr Pro Arg Ser Leu Ser Tyr Gly Ala Ile Gly Val

Ile Val Gly His Glu Phe Thr His Gly Phe Asp Asn Asn Gly Arg Lys

570

550

Glu Lys Phe Lys Glu Lys Thr Lys Cys Met Ile Asn Gln Tyr Ser Asn 610 620

Tyr Tyr Trp Lys Lys Ala Gly Leu Asn Val Lys Gly Lys Arg Thr Leu 625 630 635 640

Gly Glu Asn Ile Ala Asp Asn Gly Gly Leu Arg Glu Ala Phe Arg Ala 645 650 655

Tyr Arg Lys Trp Ile Asn Asp Arg Gln Gly Leu Glu Glu Pro Leu 660 665 670

Leu Pro Gly Ile Thr Phe Thr Asn Asn Gln Leu Phe Phe Leu Ser Tyr 675 680 685

Ala His Val Arg Cys Asn Ser Tyr Arg Pro Glu Ala Arg Glu Gln 690 695 700

Val Gln Ile Gly Ala His Ser Pro Pro Gln Phe Arg Val Asn Gly Ala 705 710 715 720

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<212> PRT

<213> Homo sapiens

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Leu Phe Tyr Asn Phe Gln Asn Cys Gly Pro Arg Pro Cys Glu Thr Ser
65 70 75 80

Val Cys Leu Asp Leu Arg Asp His Tyr Leu Ala Ser Gly Asn Thr Ser 85 90 95

Val Ala Pro Cys Thr Asp Phe Phe Ser Phe Ala Cys Gly Arg Ala Lys
100 105 110

Glu Thr Asn Asn Ser Phe Gln Glu Leu Ala Thr Lys Asn Lys Asn Arg

Leu Arg Arg Ile Leu Glu Val Gln Asn Ser Trp His Pro Gly Ser Gly 135 Glu Glu Lys Ala Phe Gln Phe Tyr Asn Ser Cys Met Asp Thr Leu Ala 150 155 Ile Glu Ala Ala Gly Thr Gly Pro Leu Arg Gln Val Ile Glu Glu Leu Gly Gly Trp Arg Ile Ser Gly Lys Trp Thr Ser Leu Asn Phe Asn Arg 185 Thr Leu Arg Leu Leu Met Ser Gln Tyr Gly His Phe Pro Phe Arg Ala Tyr Leu Gly Pro His Pro Ala Ser Pro His Thr Pro Val Ile Gln 215 Ile Asp Gln Pro Glu Phe Asp Val Pro Leu Lys Gln Asp Gln Glu Gln 230 Lys Ile Tyr Ala Gln Ile Phe Arg Glu Tyr Leu Thr Tyr Leu Asn Gln Leu Gly Thr Leu Leu Gly Gly Asp Pro Ser Lys Val Gln Glu His Ser Ser Leu Ser Ile Ser Ile Thr Ser Arg Leu Phe Gln Phe Leu Arg Pro 280 Leu Glu Gln Arg Arg Ala Gln Gly Lys Leu Phe Gln Met Val Thr Ile 290 Asp Gln Leu Lys Glu Met Ala Pro Ala Ile Asp Trp Leu Ser Cys Leu 310 Gln Ala Thr Phe Thr Pro Met Ser Leu Ser Pro Ser Gln Ser Leu Val 325 330 Val His Asp Val Glu Tyr Leu Lys Asn Met Ser Gln Leu Val Glu Glu 345 Met Leu Leu Lys Gln Arg Asp Phe Leu Gln Ser His Met Ile Leu Gly 360 Leu Val Val Thr Leu Ser Pro Ala Leu Asp Ser Gln Phe Gln Glu Ala Arg Arg Lys Leu Ser Gln Lys Leu Arg Glu Leu Thr Glu Gln Pro Pro 390 Met Pro Ala Arg Pro Arg Trp Met Lys Cys Val Glu Glu Thr Gly Thr Phe Phe Glu Pro Thr Leu Ala Ala Leu Phe Val Arg Glu Ala Phe Gly

Pro Ser Thr Arg Ser Ala Ala Met Lys Leu Phe Thr Ala Ile Arg Asp 440 Ala Leu Ile Thr Arg Leu Arg Asn Leu Pro Trp Met Asn Glu Glu Thr Gln Asn Met Ala Gln Asp Lys Val Ala Gln Leu Gln Val Glu Met Gly Ala Ser Glu Trp Ala Leu Lys Pro Glu Leu Ala Arg Gln Glu Tyr Asn 490 Asp Ile Gln Leu Gly Ser Ser Phe Leu Gln Ser Val Leu Ser Cys Val Arg Ser Leu Arg Ala Arg Ile Val Gln Ser Phe Leu Gln Pro His Pro 520 Gln His Arg Trp Lys Val Ser Pro Trp Asp Val Asn Ala Tyr Tyr Ser Val Ser Asp His Val Val Phe Pro Ala Gly Leu Leu Gln Pro Pro Phe Phe His Pro Gly Tyr Pro Arg Ala Val Asn Phe Gly Ala Ala Gly Ser Ile Met Ala His Glu Leu Leu His Ile Phe Tyr Gln Leu Leu Leu Pro Gly Gly Cys Leu Ala Cys Asp Asn His Ala Leu Gln Glu Ala His 600 Leu Cys Leu Lys Arg His Tyr Ala Ala Phe Pro Leu Pro Ser Arg Thr Ser Phe Asn Asp Ser Leu Thr Phe Leu Glu Asn Ala Ala Asp Val Gly 625 630 635 Gly Leu Ala Ile Ala Leu Gln Ala Tyr Ser Lys Arg Leu Leu Arg His His Gly Glu Thr Val Leu Pro Ser Leu Asp Leu Ser Pro Gln Gln Ile Phe Phe Arg Ser Tyr Ala Gln Val Met Cys Arg Lys Pro Ser Pro Gln Asp Ser His Asp Thr His Ser Pro Pro His Leu Arg Val His Gly Pro Leu Ser Ser Thr Pro Ala Phe Ala Arg Tyr Phe Arg Cys Ala Arg Gly Ala Leu Leu Asn Pro Ser Ser Arg Cys Gln Leu Trp

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Glu Lys Arg Leu Val Val Leu Val Leu Leu Ala Ala Gly Leu Val
50 60

Ala Cys Leu Ala Ala Leu Gly Ile Gln Tyr Gln Thr Arg Ser Pro Ser 65 70 75 80

Val Cys Leu Ser Glu Ala Cys Val Ser Val Thr Ser Ser Ile Leu Ser 85 90 95

Ser Met Asp Pro Thr Val Asp Pro Cys His Asp Phe Phe Ser Tyr Ala 100 105 110

Cys Gly Gly Trp Ile Lys Ala Asn Pro Val Pro Asp Gly His Ser Arg 115 120 125

Trp Gly Thr Phe Ser Asn Leu Trp Glu His Asn Gln Ala Ile Ile Lys 130 135

His Leu Leu Glu Asn Ser Thr Ala Ser Val Ser Glu Ala Glu Arg Lys
145 150 155 160

Ala Gln Val Tyr Tyr Arg Ala Cys Met Asn Glu Thr Arg Ile Glu Glu 165 170 175

Leu Arg Ala Lys Pro Leu Met Glu Leu Ile Glu Arg Leu Gly Gly Trp
180 185 190

Asn Ile Thr Gly Pro Trp Ala Lys Asp Asn Phe Gln Asp Thr Leu Gln

Val Val Thr Ala His Tyr Arg Thr Ser Pro Phe Phe Ser Val Tyr Val 210 215 220

Ser Ala Asp Ser Lys Asn Ser Asn Ser Asn Val Ile Gln Val Asp Gln 225 230 235 240

Ser Gly Leu Gly Leu Pro Ser Arg Asp Tyr Tyr Leu Asn Lys Thr Glu

Asn Glu Lys Val Leu Thr Gly Tyr Leu Asn Tyr Met Val Gln Leu Gly 260 265 270

Lys Leu Leu Gly Gly Gly Asp Glu Glu Ala Ile Arg Pro Gln Met Gln 275 280 285

Gln Ile Leu Asp Phe Glu Thr Ala Leu Ala Asn Ile Thr Ile Pro Gln 290 295 300

Glu Lys Arg Arg Asp Glu Glu Leu Ile Tyr His Lys Val Thr Ala Ala 305 310 315

Glu Leu Gln Thr Leu Ala Pro Ala Ile Asn Trp Leu Pro Phe Leu Asn 325 330 335

Thr Ile Phe Tyr Pro Val Glu Ile Asn Glu Ser Glu Pro Ile Val Val 340 345 350

Tyr Asp Lys Glu Tyr Leu Glu Gln Ile Ser Thr Leu Ile Asn Thr Thr 355 360 365

Asp Arg Cys Leu Leu Asn Asn Tyr Met Ile Trp Asn Leu Val Arg Lys 370 375 380

Thr Ser Ser Phe Leu Asp Gln Arg Phe Gln Asp Ala Asp Glu Lys Phe 385 390 395 400

Met Glu Val Met Tyr Gly Thr Lys Lys Thr Cys Leu Pro Arg Trp Lys 405 410 415

Phe Cys Val Ser Asp Thr Glu Asn Asn Leu Gly Phe Ala Leu Gly Pro 420 425 430

Met Phe Val Lys Ala Thr Phe Ala Glu Asp Ser Lys Ser Ile Ala Thr 435 440 445

Glu Ile Ile Leu Glu Ile Lys Lys Ala Phe Glu Glu Ser Leu Ser Thr 450 455 460

Leu Lys Trp Met Asp Glu Glu Thr Arg Lys Ser Ala Lys Glu Lys Ala 465 470 475 480

Asp Ala Ile Tyr Asn Met Ile Gly Tyr Pro Asn Phe Ile Met Asp Pro 485 490 495

Lys Glu Leu Asp Lys Val Phe Asn Asp Tyr Thr Ala Val Pro Asp Leu 500 505 510

Tyr Phe Glu Asn Ala Met Arg Phe Phe Asn Phe Ser Trp Arg Val Thr 515 520 525

Ala Asp Gln Leu Arg Lys Ala Pro Asn Arg Asp Gln Trp Ser Met Thr 530 540

Pro Pro Met Val Asn Ala Tyr Tyr Ser Pro Thr Lys Asn Glu Ile Val 545 550 555 560

Phe Pro Ala Gly Ile Leu Gln Ala Pro Phe Tyr Thr Arg Ser Ser Pro 565 570 Lys Ala Leu Asn Phe Gly Gly Ile Gly Val Val Gly His Glu Leu Thr His Ala Phe Asp Asp Gln Gly Arg Glu Tyr Asp Lys Asp Gly Asn Leu Arg Pro Trp Trp Lys Asn Ser Ser Val Glu Ala Phe Lys Arg Gln 615 Thr Glu Cys Met Val Glu Gln Tyr Ser Asn Tyr Ser Val Asn Gly Glu 630 Pro Val Asn Gly Arg His Thr Leu Gly Glu Asn Ile Ala Asp Asn Gly 650 Gly Leu Lys Ala Ala Tyr Arg Ala Tyr Gln Asn Trp Val Lys Lys Asn Gly Ala Glu His Ser Leu Pro Thr Leu Gly Leu Thr Asn Asn Gln Leu Phe Phe Leu Gly Phe Ala Gln Val Trp Cys Ser Val Arg Thr Pro Glu Ser Ser His Glu Gly Leu Ile Thr Asp Pro His Ser Pro Ser Arg Phe 710 Arg Val Ile Gly Ser Leu Ser Asn Ser Lys Glu Phe Ser Glu His Phe 725 730 Arg Cys Pro Pro Gly Ser Pro Met Asn Pro Pro His Lys Cys Glu Val 750 740 745

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170 175 180

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_			_	_	tca Ser		_		_				_	_		1168
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					tac Tyr 365											1456
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Met Val Glu Arg Ala Gly Trp Cys Arg Lys Lys Ser Pro Gly Phe Val

Glu Tyr Gly Leu Met Val Leu Leu Leu Leu Leu Gly Ala Ile Val

Thr Leu Gly Val Phe Tyr Ser Ile Gly Lys Gln Leu Pro Leu Leu Thr Ser Leu Leu His Phe Ser Trp Asp Glu Arg Thr Val Val Lys Arg Ala Leu Arg Asp Ser Ser Leu Lys Ser Asp Ile Cys Thr Thr Pro Ser Cys Val Ile Ala Ala Arg Ile Leu Glu Asn Met Asp Gln Ser Arg Asn Pro Cys Glu Asn Phe Tyr Gln Tyr Ala Cys Gly Gly Trp Leu Arg His His Val Ile Pro Glu Thr Asn Ser Arg Tyr Ser Val Phe Asp Ile Leu 120 Arg Asp Glu Leu Glu Val Ile Leu Lys Gly Val Leu Glu Asp Ser Thr Ser Gln His Arg Pro Ala Val Glu Lys Ala Lys Thr Leu Tyr Arg Ser Cys Met Asn Gln Ser Val Ile Glu Lys Arg Asp Ser Glu Pro Leu Leu Ser Val Leu Lys Met Val Gly Gly Trp Pro Val Ala Met Asp Lys Trp Asn Glu Thr Met Gly Leu Lys Trp Glu Leu Glu Arg Gln Leu Ala Val 200 Leu Asn Ser Gln Phe Asn Arg Arg Val Leu Ile Asp Leu Phe Ile Trp Asn Asp Asp Gln Asn Ser Ser Arg His Val Ile Tyr Ile Asp Gln Pro 225 230 235 Thr Leu Gly Met Pro Ser Arg Glu Tyr Tyr Phe Gln Glu Asp Asn Asn 250 His Lys Val Arg Lys Ala Tyr Leu Glu Phe Met Thr Ser Val Ala Thr Met Leu Arg Lys Asp Gln Asn Leu Ser Lys Glu Ser Ala Met Val Arg Glu Glu Met Ala Glu Val Leu Glu Leu Glu Thr His Leu Ala Asn Ala Thr Val Pro Gln Glu Lys Arg His Asp Val Thr Ala Leu Tyr His Arg Met Asp Leu Met Glu Leu Gln Glu Arg Phe Gly Leu Lys Gly Phe Asn

Trp Thr Leu Phe Ile Gln Asn Val Leu Ser Ser Val Glu Val Glu Leu Phe Pro Asp Glu Glu Val Val Tyr Gly Ile Pro Tyr Leu Glu Asn 360 Leu Glu Asp Ile Ile Asp Ser Tyr Ser Ala Arg Thr Met Gln Asn Tyr Leu Val Trp Arg Leu Val Leu Asp Arg Ile Gly Ser Leu Ser Gln Arg 390 395 Phe Lys Glu Ala Arg Val Asp Tyr Arg Lys Ala Leu Tyr Gly Thr Thr Val Glu Glu Val Arg Trp Arg Glu Cys Val Ser Tyr Val Asn Ser Asn 425 Met Glu Ser Ala Val Gly Ser Leu Tyr Ile Lys Arg Ala Phe Ser Lys Asp Ser Lys Ser Thr Val Arg Glu Leu Ile Glu Lys Ile Arg Ser Val Phe Val Asp Asn Leu Asp Glu Leu Asn Trp Met Asp Glu Glu Ser Lys 475 465 470 Lys Lys Ala Gln Glu Lys Ala Met Asn Ile Arg Glu Gln Ile Gly Tyr 490 Pro Asp Tyr Ile Leu Glu Asp Asn Asn Lys His Leu Asp Glu Glu Tyr 500 505 Ser Ser Leu Thr Phe Tyr Glu Asp Leu Tyr Phe Glu Asn Gly Leu Gln 520 Asn Leu Lys Asn Asn Ala Gln Arg Ser Leu Lys Lys Leu Arg Glu Lys 535 Val Asp Gln Asn Leu Trp Ile Ile Gly Ala Ala Val Val Asn Ala Phe Tyr Ser Pro Asn Arg Asn Gln Ile Val Phe Pro Ala Gly Ile Leu Gln 570 Pro Pro Phe Phe Ser Lys Asp Gln Pro Gln Ser Leu Asn Phe Gly Gly Ile Gly Met Val Ile Gly His Glu Ile Thr His Gly Phe Asp Asp Asn 600 Gly Arg Asn Phe Asp Lys Asn Gly Asn Met Leu Asp Trp Trp Ser Asn Phe Ser Ala Arg His Phe Gln Gln Gln Ser Gln Cys Met Ile Tyr Gln

625	630	635	640

Tyr Gly Asn Phe Ser Trp Glu Leu Ala Asp Asn Gln Asn Val Asn Gly 645 650 655

Phe Ser Thr Leu Gly Glu Asn Ile Ala Asp Asn Gly Gly Val Arg Gln 660 665 670

Ala Tyr Lys Ala Tyr Leu Arg Trp Leu Ala Asp Gly Gly Lys Asp Gln 675 680 685

Arg Leu Pro Gly Leu Asn Leu Thr Tyr Ala Gln Leu Phe Phe Ile Asn 690 695 700

Tyr Ala Gln Val Trp Cys Gly Ser Tyr Arg Pro Glu Phe Ala Val Gln 705 710 715 720

Ser Ile Lys Thr Asp Val His Ser Pro Leu Lys Tyr Arg Val Leu Gly
725 730 735

Ser Leu Gln Asn Leu Pro Gly Phe Ser Glu Ala Phe His Cys Pro Arg
740 745 750

Gly Ser Pro Met His Pro Met Lys Arg Cys Arg Ile Trp 755 760 765

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<211> 2676

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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48

ttc ctg gag ggg ggg ctg ctg ctg ctg ctg ctg ctg gtg acc gct gcc 96
Phe Leu Glu Gly Gly Leu Leu Leu Leu Leu Leu Val Thr Ala Ala
15 20 25 30

ctg gtg gcc ttg ggt gtc ctc tac gcc gac cgc aga ggg aag cag ctg 144 Leu Val Ala Leu Gly Val Leu Tyr Ala Asp Arg Arg Gly Lys Gln Leu 35 40 45

cca cgc ctt gct agc cgg ctg tgc ttc tta cag gag gag agg acc ttt 192
Pro Arg Leu Ala Ser Arg Leu Cys Phe Leu Gln Glu Glu Arg Thr Phe
50 55 60

gta aaa cga aaa ccc cga ggg atc cca gag gcc caa gag gtg agc gag 240 Val Lys Arg Lys Pro Arg Gly Ile Pro Glu Ala Gln Glu Val Ser Glu 65 70 75

				ggc Gly										288
	_	_	_	acg Thr 100	_	_	_	_	_					336
				cgg Arg										384
				gtc Val										432
		_		tcg Ser		_	_	_		_	_	_		480
_		_	_	cgc Arg										528
				ctg Leu 180										576
				agg Arg										624
				gcg Ala										672
				atc Ile										720
				cag Gln										768
				agc Ser 260										816
				gcc Ala										864
				gtg Val										912

							acg Thr 310									960
							atg Met									1008
							tgg Trp									1056
		_			_	_	ctg Leu									1104
							ctt Leu									1152
							ctg Leu 390									1200
							ttc Phe									1248
							gtg Val									1296
							atg Met									1344
							gac Asp									1392
att Ile	gac Asp	aag Lys 465	gtg Val	cgg Arg	aca Thr	gtg Val	ttt Phe 470	gtg Val	gag Glu	acg Thr	ctg Leu	gac Asp 475	gag Glu	ctg Leu	ggc Gly	1440
							aag Lys									1488
							cct Pro									1536
							tcc Ser									1584
tac	ttt	gag	aac	agt	ctg	cag	aac	ctc	aag	gtg	ggc	gcc	cag	cgg	agc	1632

Tyr Phe Glu Asn Ser Leu Gln Asn Leu Lys Val Gly Ala Gln Arg Ser 530 535 ctc agg aag ctt cgg gaa aag gtg gac cca aat ctc tgg atc atc ggg 1680 Leu Arg Lys Leu Arg Glu Lys Val Asp Pro Asn Leu Trp Ile Ile Gly 550 gcg gcg gtg gtc aat gcg ttc tac tcc cca aac cga aac cag att gta 1728 Ala Ala Val Val Asn Ala Phe Tyr Ser Pro Asn Arg Asn Gln Ile Val 565 560 ttc cct gcc ggg atc ctc cag ccc ccc ttc ttc agc aag gag cag cca 1776 Phe Pro Ala Gly Ile Leu Gln Pro Pro Phe Phe Ser Lys Glu Gln Pro 575 580 585 cag gcc ttg aac ttt gga ggc att ggg atg gtg atc ggg cac gag atc 1824 Gln Ala Leu Asn Phe Gly Gly Ile Gly Met Val Ile Gly His Glu Ile 600 595 acq cac qqc ttt qac qac aat qqc cqq aac ttc gac aag aat ggc aac 1872 Thr His Gly Phe Asp Asp Asn Gly Arg Asn Phe Asp Lys Asn Gly Asn 615 atg atg gat tgg tgg agt aac ttc tcc acc cag cac ttc cgg gag cag Met Met Asp Trp Trp Ser Asn Phe Ser Thr Gln His Phe Arg Glu Gln 625 tca gag tgc atg atc tac cag tac ggc aac tac tcc tgg gac ctg gca Ser Glu Cys Met Ile Tyr Gln Tyr Gly Asn Tyr Ser Trp Asp Leu Ala 640 645 gac gaa cag aac gtg aac gga ttc aac acc ctt ggg gaa aac att gct 2016 Asp Glu Gln Asn Val Asn Gly Phe Asn Thr Leu Gly Glu Asn Ile Ala 655 660 670 gac aac gga ggg gtg cgg caa gcc tat aag gcc tac ctc aag tgg atg 2064 Asp Asn Gly Gly Val Arg Gln Ala Tyr Lys Ala Tyr Leu Lys Trp Met 675 680 qca qaq qqt qqc aaq qac caq caq ctq ccc ggc ctg gat ctc acc cat 2112 Ala Glu Gly Gly Lys Asp Gln Gln Leu Pro Gly Leu Asp Leu Thr His 690 gag cag ctc ttc ttc atc aac tat gcc cag gtg tgg tgc ggg tcc tac 2160 Glu Gln Leu Phe Phe Ile Asn Tyr Ala Gln Val Trp Cys Gly Ser Tyr 705 cgg ccc gag ttc gcc atc caa tcc atc aag aca gac gtc cac agt ccc 2208 Arg Pro Glu Phe Ala Ile Gln Ser Ile Lys Thr Asp Val His Ser Pro 720 725 ctg aag tac agg gta ctg ggg tcg ctg cag aac ctg gcc gcc ttc gca 2256 Leu Lys Tyr Arg Val Leu Gly Ser Leu Gln Asn Leu Ala Ala Phe Ala gac acg ttc cac tgt gcc cgg ggc acc ccc atg cac ccc aag gag cga 2304 Asp Thr Phe His Cys Ala Arg Gly Thr Pro Met His Pro Lys Glu Arg

755 760 765

2356

tgc cgc gtg tgg tagccaaggc cctgccgcgc tgtgcggccc acgcccaccc Cys Arg Val Trp 770

gctgctcgga ggcatctgtg cgaaggtgca gctagcggcg acccagtgta cgtcccgccc 2416 cggccaacca tgccaagcct gcctgccagg cctctgcgcc tggcctaggg tgcagccacc 2476 tgcctgacac ccagggatga gcagtgtcca gtgcagtacc tggaccggag cccccttcac 2536 agacacccgc ggggctcagt gcccccgtca caactctgta gagacaatca actgtgtcct 2596 gcccaccctt caaggtgcat tgtcttccag tatctacagc ttcagaactt gagctaagta 2656 aatgctttca aagaaaaaaa

<210> 15

<211> 770

<212> PRT

<213> Homo sapiens

<400> 15

Met Val Glu Ser Ala Gly Arg Ala Gly Gln Lys Arg Pro Gly Phe Leu
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Glu Gly Gly Leu Leu Leu Leu Leu Leu Val Thr Ala Ala Leu Val
20 25 30

Ala Leu Gly Val Leu Tyr Ala Asp Arg Arg Gly Lys Gln Leu Pro Arg 35 40 45

Leu Ala Ser Arg Leu Cys Phe Leu Gln Glu Glu Arg Thr Phe Val Lys
50 55 60

Arg Lys Pro Arg Gly Ile Pro Glu Ala Gln Glu Val Ser Glu Val Cys 65 70 75 80

Thr Thr Pro Gly Cys Val Ile Ala Ala Ala Arg Ile Leu Gln Asn Met 85 90 95

Asp Pro Thr Thr Glu Pro Cys Asp Asp Phe Tyr Gln Phe Ala Cys Gly
100 105 110

Gly Trp Leu Arg Arg His Val Ile Pro Glu Thr Asn Ser Arg Tyr Ser 115 120 125

Ile Phe Asp Val Leu Arg Asp Glu Leu Glu Val Ile Leu Lys Ala Val 130 135 140

Leu Glu Asn Ser Thr Ala Lys Asp Arg Pro Ala Val Glu Lys Ala Arg 145 150 155 160

Thr Leu Tyr Arg Ser Cys Met Asn Gln Ser Val Ile Glu Lys Arg Gly
165 170 175

Ser Gln Pro Leu Leu Asp Ile Leu Glu Val Val Gly Gly Trp Pro Val 180 185 190

Ala Met Asp Arg Trp Asn Glu Thr Val Gly Leu Glu Trp Glu Leu Glu
195 200 205

Arg Gln Leu Ala Leu Met Asn Ser Gln Phe Asn Arg Arg Val Leu Ile 210 215 220

Asp Leu Phe Ile Trp Asn Asp Asp Gln Asn Ser Ser Arg His Ile Ile 225 230 235 240

Tyr Ile Asp Gln Pro Thr Leu Gly Met Pro Ser Arg Glu Tyr Tyr Phe 245 250 255

Asn Gly Gly Ser Asn Arg Lys Val Arg Glu Ala Tyr Leu Gln Phe Met 260 265 270

Val Ser Val Ala Thr Leu Leu Arg Glu Asp Ala Asn Leu Pro Arg Asp 275 280 285

Ser Cys Leu Val Gln Glu Asp Met Val Gln Val Leu Glu Leu Glu Thr 290 295 300

Gln Leu Ala Lys Ala Thr Val Pro Gln Glu Glu Arg His Asp Val Ile 305 310 315 320

Ala Leu Tyr His Arg Met Gly Leu Glu Glu Leu Gln Ser Gln Phe Gly 325 330 335

Leu Lys Gly Phe Asn Trp Thr Leu Phe Ile Gln Thr Val Leu Ser Ser

Val Lys Ile Lys Leu Leu Pro Asp Glu Glu Val Val Tyr Gly Ile 355 360 365

Pro Tyr Leu Gln Asn Leu Glu Asn Ile Ile Asp Thr Tyr Ser Ala Arg 370 375 380

Thr Ile Gln Asn Tyr Leu Val Trp Arg Leu Val Leu Asp Arg Ile Gly 385 390 395 400

Ser Leu Ser Gln Arg Phe Lys Asp Thr Arg Val Asn Tyr Arg Lys Ala 405 410 415

Leu Phe Gly Thr Met Val Glu Glu Val Arg Trp Arg Glu Cys Val Gly 420 425 430

Tyr Val Asn Ser Asn Met Glu Asn Ala Val Gly Ser Leu Tyr Val Arg 435 440 445

Glu Ala Phe Pro Gly Asp Ser Lys Ser Met Val Arg Glu Leu Ile Asp 450 455 460

Lys Val Arg Thr Val Phe Val Glu Thr Leu Asp Glu Leu Gly Trp Met 465 470 475 480

Asp Glu Glu Ser Lys Lys Lys Ala Gln Glu Lys Ala Met Ser Ile Arg 490 Glu Gln Ile Gly His Pro Asp Tyr Ile Leu Glu Glu Met Asn Arg Arg Leu Asp Glu Glu Tyr Ser Asn Leu Asn Phe Ser Glu Asp Leu Tyr Phe 520 Glu Asn Ser Leu Gln Asn Leu Lys Val Gly Ala Gln Arg Ser Leu Arg 535 Lys Leu Arg Glu Lys Val Asp Pro Asn Leu Trp Ile Ile Gly Ala Ala 550 555 Val Val Asn Ala Phe Tyr Ser Pro Asn Arg Asn Gln Ile Val Phe Pro 570 Ala Gly Ile Leu Gln Pro Pro Phe Phe Ser Lys Glu Gln Pro Gln Ala Leu Asn Phe Gly Gly Ile Gly Met Val Ile Gly His Glu Ile Thr His Gly Phe Asp Asp Asn Gly Arg Asn Phe Asp Lys Asn Gly Asn Met Met 615 Asp Trp Trp Ser Asn Phe Ser Thr Gln His Phe Arg Glu Gln Ser Glu 625 630 635 Cys Met Ile Tyr Gln Tyr Gly Asn Tyr Ser Trp Asp Leu Ala Asp Glu 645 650 Gln Asn Val Asn Gly Phe Asn Thr Leu Gly Glu Asn Ile Ala Asp Asn 660 Gly Gly Val Arq Gln Ala Tyr Lys Ala Tyr Leu Lys Trp Met Ala Glu 680 Gly Gly Lys Asp Gln Gln Leu Pro Gly Leu Asp Leu Thr His Glu Gln Leu Phe Phe Ile Asn Tyr Ala Gln Val Trp Cys Gly Ser Tyr Arg Pro Glu Phe Ala Ile Gln Ser Ile Lys Thr Asp Val His Ser Pro Leu Lys 730 Tyr Arg Val Leu Gly Ser Leu Gln Asn Leu Ala Ala Phe Ala Asp Thr Phe His Cys Ala Arg Gly Thr Pro Met His Pro Lys Glu Arg Cys Arg 760

Val Trp 770 <210> 16 <211> 2871 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (205)..(2529) <400> 16 cgaccegete ggteacegee ggetegggeg egeacetgee ggetgeggee ceagggecat 120 qcqqaqgccc acgaggaggc cggcggccac gcgcatcccg tagcccaggt ggcccaggtc 180 tgcaccgcqq cqqcctcqqc qccq atg gag ccc ccg tat tcg ctg acg gcg 231 Met Glu Pro Pro Tyr Ser Leu Thr Ala cac tac gat gag ttc caa gag gtc aag tac gtg agc cgc tgc ggc gcg His Tyr Asp Glu Phe Gln Glu Val Lys Tyr Val Ser Arg Cys Gly Ala 10 15 ggg ggc gcg cgc ggg gcc tcc ctg ccc ccg ggc ttc ccg ttg ggc gct Gly Gly Ala Arg Gly Ala Ser Leu Pro Pro Gly Phe Pro Leu Gly Ala 3.0 35 40 geg ege age gee ace ggg gee egg tee ggg etg eeg ege tgg aac egg Ala Arg Ser Ala Thr Gly Ala Arg Ser Gly Leu Pro Arg Trp Asn Arg 45 55 423 Arg Glu Val Cys Leu Leu Ser Gly Leu Val Phe Ala Ala Gly Leu Cys 60 65 ged att etg geg get atg etg ged etd aag tad etg ggd eeg gtd geg 471 Ala Ile Leu Ala Ala Met Leu Ala Leu Lys Tyr Leu Gly Pro Val Ala 75 gee gge gge gge tgt eee gag gge tge eet gag ege aag gee tte 519 Ala Gly Gly Gly Ala Cys Pro Glu Gly Cys Pro Glu Arg Lys Ala Phe 90 95 105 geg ege get ege tte etg gee gee aac etg gae gee age ate gae 567 Ala Arg Ala Arg Phe Leu Ala Ala Asn Leu Asp Ala Ser Ile Asp 110 cca tgc cag gac ttc tac tcg ttc gcc tgc ggc ggt tgg ctg cgc 615 Pro Cys Gln Asp Phe Tyr Ser Phe Ala Cys Gly Gly Trp Leu Arg Arg 130 125 663 cac gcc atc ccc gac gac aag ctc acc tat ggc acc atc gcg gca atc His Ala Ile Pro Asp Asp Lys Leu Thr Tyr Gly Thr Ile Ala Ala Ile

140 145 150

												ccc Pro		711
												ttc Phe		759
												ccc Pro 200		807
				 _				_	_			gcg Ala	_	855
												ctg Leu		903
			 	_	_	_						acg Thr	_	951
												gac Asp		999
_			_				_			_	_	gat Asp 280	_	1047
												cga Arg		1095
												gag Glu		1143
												tat Tyr		1191
												ctg Leu		1239
_	_	_				_			_		_	cta Leu 360	_	1287
												ctg Leu		1335

					cag Gln											1383
					aac Asn											1431
					ccg Pro 415											1479
_		_			agc Ser	_	_		_	-						1527
_		_	_		cgc Arg				_				_			1575
_					tca Ser	_	_	_		-	_		_	_		1623
					tac Tyr											1671
	_	_	_		acc Thr 495		_	_	_		_	_		_		1719
					ggc Gly											1767
					gag Glu											1815
			aac	aqc	atc	cqc	ttc	agc	atc	caq	ctc	tca	gtt			1863
	Ile	Leu 540	Asn	Ser	Ile	Arg	Phe 545					Ser 550	Val	Lys	Lys	
	cgg	540 cag	gag	gtg	Ile gac Asp	aag	545 tcc	Ser	Ile tgg	Gln	Leu ctc	550 ccc	сса	cag	gcg	1911
Ile	cgg Arg 555 aat	cag Gln	gag Glu tac	gtg Val tat	gac	aag Lys 560	545 tcc Ser	ser acg Thr	Ile tgg Trp	Gln ctg Leu cag	ctc Leu 565 atg	550 ccc Pro	cca Pro	cag Gln	gcg Ala gcg	1911 1959

														cac His		2055
														ctg Leu		2103
														gag Glu		2151
														gtg Val		2199
														ctc Leu 680		2247
														cca Pro		2295
														ttc Phe		2343
														atc Ile		2391
														gtg Val		2439
														tgt Cys 760		2487
_	_			_			gcc Ala		_	_		_				2529
tgad	ccct	ggc t	tgcc	egect	tg ca	acgco	ccca	a cts	gccc	ccgc	acga	aatca	acc	tcct	gctggc	2589
tac	9999	gca q	ggcai	tgca	cc c9	ggtgo	ccago	c cc	cgct	ctgg	gca	ccac	ctg	cctt	ccagcc	2649
cct	ccago	gac d	ccggt	tccc	ec to	gctgo	cccct	cac	cttca	agga	ggg	gcct	gga	gcag	ggtgag	2709
gct	ggact	ttt 🤉	gggg	ggct	gt ga	aggga	aaata	a tad	ctgg	ggtc	ccca	agatt	tct	gctct	aaggg	2769
ggc	caga	ccc 1	tctg	ccag	gc to	ggatt	gtad	ggs	gccc	cacc	ttc	gctgt	tgt	tctt	gctgca	2829
agto	ctggt	ca a	aataa	aatca	ac to	gcact	gtta	a aaa	aaaa	aaaa	aa					2871

<210> 17

<211> 775

<212> PRT

<213> Homo sapiens

<400> 17

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Val Lys Tyr Val Ser Arg Cys Gly Ala Gly Gly Ala Arg Gly Ala Ser 20 25 30

Leu Pro Pro Gly Phe Pro Leu Gly Ala Ala Arg Ser Ala Thr Gly Ala 35 40 45

Arg Ser Gly Leu Pro Arg Trp Asn Arg Arg Glu Val Cys Leu Leu Ser 50 60

Gly Leu Val Phe Ala Ala Gly Leu Cys Ala Ile Leu Ala Ala Met Leu 65 70 75 80

Ala Leu Lys Tyr Leu Gly Pro Val Ala Ala Gly Gly Ala Cys Pro 85 90 95

Glu Gly Cys Pro Glu Arg Lys Ala Phe Ala Arg Ala Arg Phe Leu 100 105 110

Ala Ala Asn Leu Asp Ala Ser Ile Asp Pro Cys Gln Asp Phe Tyr Ser 115 120 125

Phe Ala Cys Gly Gly Trp Leu Arg Arg His Ala Ile Pro Asp Asp Lys 130 135

Leu Thr Tyr Gly Thr Ile Ala Ala Ile Gly Glu Gln Asn Glu Glu Arg 145 150 155 160

Leu Arg Arg Leu Leu Ala Arg Pro Gly Gly Gly Pro Gly Gly Ala Ala 165 170 175

Gln Arg Lys Val Arg Ala Phe Phe Arg Ser Cys Leu Asp Met Arg Glu 180 185 190

Ile Glu Arg Leu Gly Pro Arg Pro Met Leu Glu Val Ile Glu Asp Cys 195 200 205

Gly Gly Trp Asp Leu Gly Gly Ala Glu Glu Arg Pro Gly Val Ala Ala 210 215 220

Arg Trp Asp Leu Asn Arg Leu Leu Tyr Lys Ala Gln Gly Val Tyr Ser 225 230 235 240

Ala Ala Leu Phe Ser Leu Thr Val Ser Leu Asp Asp Arg Asn Ser

Ser Arg Tyr Val Ile Arg Ile Asp Gln Asp Gly Leu Thr Leu Pro Glu 260 265 270 Arg Thr Leu Tyr Leu Ala Gln Asp Glu Asp Ser Glu Lys Val Leu Ala 275 280 285

Ala Tyr Arg Val Phe Met Glu Arg Val Leu Ser Leu Leu Gly Ala Asp 290 295 300

Ala Val Glu Gln Lys Ala Gln Glu Ile Leu Gln Val Glu Gln Gln Leu 305 310 315 320

Ala Asn Ile Thr Val Ser Glu Tyr Asp Asp Leu Arg Arg Asp Val Ser 325 330 335

Ser Met Tyr Asn Lys Val Thr Leu Gly Gln Leu Gln Lys Ile Thr Pro 340 345 350

His Leu Arg Trp Lys Trp Leu Leu Asp Gln Ile Phe Gln Glu Asp Phe 355 360 365

Ser Glu Glu Glu Val Val Leu Leu Ala Thr Asp Tyr Met Gln Gln 370 375 380

Val Ser Gln Leu Ile Arg Ser Thr Pro His Arg Val Leu His Asn Tyr 385 390 395 400

Leu Val Trp Arg Val Val Val Leu Ser Glu His Leu Ser Pro Pro 405 410 415

Phe Arg Glu Ala Leu His Glu Leu Ala Gln Glu Met Glu Gly Ser Asp 420 425 430

Lys Pro Gln Glu Leu Ala Arg Val Cys Leu Gly Gln Ala Asn Arg His
435
440
445

Phe Gly Met Ala Leu Gly Ala Leu Phe Val His Glu His Phe Ser Ala 450 455 460

Ala Ser Lys Ala Lys Val Gln Gln Leu Val Glu Asp Ile Lys Tyr Ile 465 470 475 480

Leu Gly Gln Arg Leu Glu Glu Leu Asp Trp Met Asp Ala Glu Thr Arg
485 490 495

Ala Ala Arg Ala Lys Leu Gln Tyr Met Met Val Met Val Gly Tyr 500 505 510

Pro Asp Phe Leu Leu Lys Pro Asp Ala Val Asp Lys Glu Tyr Glu Phe 515 520 525

Glu Val His Glu Lys Thr Tyr Phe Lys Asn Ile Leu Asn Ser Ile Arg 530 540

Phe Ser Ile Gln Leu Ser Val Lys Lys Ile Arg Gln Glu Val Asp Lys 545 550 555 560

Ser Thr Trp Leu Pro Pro Gln Ala Leu Asn Ala Tyr Tyr Leu Pro 565 570 575

a , , ,

Asn Lys Asn Gln Met Val Phe Pro Ala Gly Ile Leu Gln Pro Thr Leu 580 585 Tyr Asp Pro Asp Phe Pro Gln Ser Leu Asn Tyr Gly Gly Ile Gly Thr Ile Ile Gly His Glu Leu Thr His Gly Tyr Asp Asp Trp Gly Gly Gln Tyr Asp Arg Ser Gly Asn Leu Leu His Trp Trp Thr Glu Ala Ser Tyr Ser Arg Phe Leu Arg Lys Ala Glu Cys Ile Val Arg Leu Tyr Asp Asn Phe Thr Val Tyr Asn Gln Arg Val Asn Gly Lys His Thr Leu Gly Glu 665 Asn Ile Ala Asp Met Gly Gly Leu Lys Leu Ala Tyr His Ala Tyr Gln 680 Lys Trp Val Arg Glu His Gly Pro Glu His Pro Leu Pro Arg Leu Lys Tyr Thr His Asp Gln Leu Phe Phe Ile Ala Phe Ala Gln Asn Trp Cys Ile Lys Arg Arg Ser Gln Ser Ile Tyr Leu Gln Val Leu Thr Asp Lys 725 His Ala Pro Glu His Tyr Arg Val Leu Gly Ser Val Ser Gln Phe Glu 740 Glu Phe Gly Arg Val Leu His Cys Pro Lys Val Ser Pro Met Asn Pro 760

Ala His Lys Cys Ser Val Trp